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CORRESPONDENCE

Analgesia Nociception Index as a phenotypic marker for cardiac autonomic activity during cold pressor test in women treated for breast cancer

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Editor—The autonomic nervous system (ANS) has an important role in endogenous pain modulation.[1] Heart rate variability (HRV) based parameters, such as Analgesia Nociception Index (ANI), are used to evaluate sympathovagal responses of the ANS to nociceptive stimuli.[2] The ANI algorithm is based on an amplitude assessment of respiratory patterns of the ventilatory frequency series.[3] Little is known about ANI in alert patients in evaluating their ANS functioning. We studied differences in ANS responses to tonic cold pain stimuli using ANI in women treated for breast cancer 4–9 yr earlier.[4] The main goal was to identify different profiles in ANS function by ANI during cold pressor test (CPT). These ANS profiles could be further explored as biomarkers against various patient- and pain-related factors.

The study protocol was approved by the local Ethics Committee (Ref. 149/13/03/00/14) and registered at ClinicalTrials.gov (NCT02487524). The subjects were recruited from a previous longitudinal cohort of 1000 women treated for breast cancer from 2006 to 2010.[5] Patients having a verified nerve injury or reporting persistent postsurgical pain were invited to join the study[4]; of the 560 invited patients, 158 declined or were lost to follow-up. Of the 402 participants, 269 were included in the final analysis. Exclusion criteria were factors (e.g. diabetes mellitus, beta-blocker use) affecting ANS regulation (n=112), poor ANI signal (n=20), or a pacemaker (n=1). Of the 269 subjects, 203 had neuropathic pain, other pain, or both, whereas 66 reported no pain. Nine subjects used neuropathic pain medications, and no other analgesics were used regularly.

All subjects underwent CPT by immersing their contralateral (to previous breast cancer surgery) hand up to the wrist into a circulating cold (2–4°C) water bath (JULABO USA Inc., Allentown, PA, USA) for as long as they could tolerate it (i.e. withdrawal time) with a cut-off at 90 s. They reported pain intensity using a Numerical Rating Scale (NRS; 0–10, where 0=no pain and 10=the worst possible pain intensity) every 15 s during the CPT and at the end of the test, followed by a rating of unpleasantness (NRS 0–10). ANS function was recorded using an ANI monitor (Mdoloris Medical System, Lille, France) throughout the CPT from 1 min before the test to 15 min after withdrawal.

The first pain ratings were collected at 15 s after the beginning of CPT. Withdrawal times were categorised by 15 s time intervals into six groups: Group 1, 15–29 s; Group 2, 30–44 s; Group 3, 45–59 s; Group 4, 60–74 s; Group 5, 75–89 s; and Group 6, 90 s. Subjects with a withdrawal time of <15 s (n=9) were excluded because matched ANI–NRS values were not obtained before the 15 s time point.

We used linear mixed modelling for unbalanced longitudinal data.[6] We studied both linear and non-linear changes in the NRS and ANI values over time by adding centred linear and quadratic components of time in the model. The unstructured covariance structure for the random effects was selected based on Bayesian information criterion. As an estimation method we used restricted maximum likelihood. Bonferroni correction was used for all *post hoc* analyses.

Age, BMI, anxiety, and depression (measured using Hospital Anxiety and Depression Scale [HADS]), systolic and diastolic BP (OMRON M10-IT; OMRON Healthcare Co., Ltd, Kyoto, Japan), ANI at baseline (defined as the time 0 s), and intensity of any chronic pain (NRS 0–10) were used as covariates. Statistical analyses were performed using SPSS 22.0 for Windows (SPSS Inc., Chicago, IL, USA).[7] Mean age was 60 yr (39–75) and mean BMI 25.2 kg m^{-2} (standard deviation [SD] 3.9). Mean systolic/diastolic blood pressure was 135/89 mm Hg. There was no clinically significant anxiety or depression.

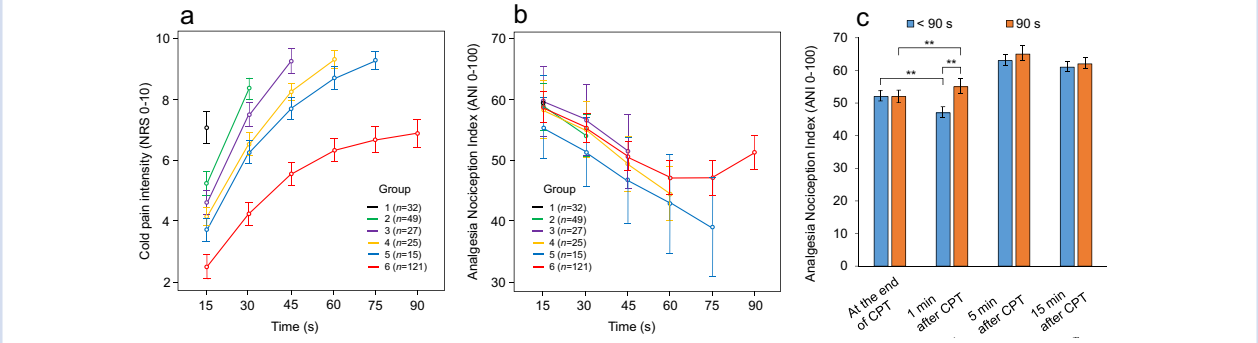

Fig 1. Mean cold pain intensity ratings and analgesia nociception index (ANI) values. (a) Mean cold pain intensity ratings (Numerical Rating Scale [NRS], 0–10) with 95% confidence intervals (CI) during the cold pressor test (CPT). In Group 6, the non-linear increase of NRS values was significantly slower compared with the other groups. (b) Mean Analgesia Nociception Index (ANI) values with 95% CI during the CPT. Patients in Group 6 first showed a decrease followed by an increase in ANI. (c) Mean ANI values with 95% CI at the end of CPT, and 1, 5, and 15 min after withdrawal. ANI values differed significantly between the groups (1–5 *vs* 6) up to 1 min after withdrawal.

During CPT, pain intensity (NRS) increased significantly over time ($F_{1,\ 798}$=62.02, p<0.001). There was a strong correlation between pain and unpleasantness at the end of CPT (r=0.51, p<0.001). The non-linear (quadratic) change of the increase of NRS values was significantly slower in Group 6 compared with the other groups ($F_{3,\ 588}$=6.72, p<0.001) (Fig. 1a). ANI values decreased in a quasi-linear fashion over time ($F_{1,\ 631}$=55.04, p<0.001). However, there was positive quadratic change ($F_{3,\ 417}$=8.51, p<0.001) in Group 6 towards the end of CPT (Fig. 1b).

At 1 min after withdrawal, ANI values differed significantly between groups (p<0.001). The time points used were end of CPT, 1, 5, and 15 min after withdrawal (mean ANI values with 95% confidence intervals). ANI values decreased at the 1 min time point in Groups 1–5 (withdrawal time, <90 s; 51.9 *vs* 47.3, p<0.001), whereas ANI values continued to increase in Group 6 (withdrawal time 90 s; 52.2 *vs* 55.5, p<0.001). The differences were stabilised in 15 min (Groups 1–5, 63.5 *vs* 61.1, t_{145}=1.88, p=0.062 and Group 6, 65.2 *vs* 62.2, t_{120}=1.91, p=0.058) (Fig. 1c). Subjects who tolerated the maximum 90 s reported lowest overall pain intensity and their ANI values increased after an initial decrease during CPT. This suggests that it takes some time for the pain inhibitory system to be activated by experimental pain (here, ~75 s).

We showed that ANS reactions to cold pain stimuli associate with pain sensitivity. However, our results may not only reflect the effect of activated nociceptors of cutaneous veins, but also the effect of cold itself on ANS. The CPT could thus evoke more unpleasantness compared with other experimental pain models.[8,9] We found different ANS functioning between CPT tolerant *vs* non-tolerant groups.

Future research will show whether profiling ANS responses to experimental pain provides new phenotypes associated with persistent postsurgical pain. A previous study suggested that better cold pain tolerance was associated with a reduced risk of persistent postsurgical pain.[10] The current results cannot be directly generalised to healthy participants or males, because our patient cohort consisted of women treated for breast cancer. This study design did not assess endogenous pain inhibition.

The present data provide further evidence for the role of the ANS in pain regulation. Further research is needed in patients with potential factors affecting ANS regulation.

Authors' contributions

Study design: EK, HH.
Data analysis: TA, JL.
Drafting of the manuscript: all authors.

Declarations of interest

EK serves in the advisory board of Orion Pharma (Helsinki, Finland) and has served in the advisory boards of Gruenenthal (Aachen, Germany) and Pierre Fabre (Toulouse, France).The other authors declare that they have no conflicts of interests.

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